Key Events and Considerations for LHP Cancers

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Evaluations of Formaldehyde and LHP Cancers

Over the last 13 years, several formaldehyde evaluations have been performed (year finalized), including the following:

- 2004: IARC Monograph 88 (2006)
- 2009: IARC Monograph 100F (2012)
- 2010: EPA DRAFT IRIS Toxicological Review (pending)
- 2012: NTP 12th Report on Carcinogens (2013)
- 2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL) (2016)

2004: IARC (Monograph 88, 2006)

Classification: Carcinogenic to humans (Group 1)

Epidemiological evidence: Sufficient, based on nasopharyngeal cancer

Leukemia: "There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers." (p.276)

(continued)

2004: IARC (Monograph 88, 2006)

Supporting data: Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells.

"The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." (p. 280)

2009: IARC Monograph 100F (2012)

Classification: Carcinogenic to humans (Group 1)(unchanged)

Epidemiological evidence: Formaldehyde causes cancer of the nasopharynx and leukaemia.

"The Working Group was not in full agreement on the evaluation of formaldehyde causing leukaemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430)

(continued)

2009: IARC Monograph 100F (2012)

Toxicological evidence: "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427)

"Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428)

"Inconsistent genotoxic effects [seen] in blood lymphocytes from animals exposed to formaldehyde via inhalation."

(continued)

2009: IARC Monograph 100F (2012)

Supporting data: "Particularly relevant. . was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430)

"Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans." (p. 430)

2010: EPA Draft IRIS Toxicological Review (2010)

Epidemiological evidence: "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (page 6-46).

(continued)

2010: EPA Draft IRIS Toxicological Review (2010)

All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (page 4-180).

(continued)

2010: EPA Draft IRIS Toxicological Review (2010)

All leukemias combined: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (page 4-182)

(continued)

2010: EPA Draft IRIS Toxicological Review (2010)

Toxicological evidence: Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde.

"Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p.6-21)

(continued)

2010: EPA Draft IRIS Toxicological Review (2010)

Supporting data: "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been docoumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p.6-22)

2012 NTP 12th RoC (2013)

Epidemiological evidence: "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans.

Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding.

The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195)

(continued)

2012 NTP 12th RoC (2013)

Toxicological evidence: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198)

(continued)

2012 NTP 12th RoC (2013)

Supporting data: "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004)."

"Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al. 2010a)."

"Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites." (p. 199)

2012: European Chemicals Agency (ECHA), Committee for Risk Assessment (RAC) (2012)

Classification: Carcinogen 1B - H50 f (May cause cancer)

Epidemiological evidence: "In conclusion, while some studies have found increased rates of leukaemia, the epidemiology data do not show consistent findings across studies for leukaemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates."

"Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukaemia." (p.41)

(continued)

2012: European Chemicals Agency (ECHA), Committee for Risk Assessment (RAC) (2012)

Toxicological evidence: "No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumours in inhalation study of rats and mice (Kerns et al. 1983)." (p.22)

Supporting data: "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations."

"These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry." (p.44)

2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016)

Epidemiological evidence: "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45)

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2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016)

Toxicological Evidence: "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49)

Supporting Data: "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)

Additional Considerations

- Science evolves, and the scientific landscape today is different from 10 years or more ago
- Where do differences persist, and why?
- Are there data gaps? Can we identify practical ways of filling them?
- If formaldehyde is/is not leukemogenic, what is the best framework for risk assessment?

Thank you.